Genetically Engineered Food
— The Unpredictable Hazards —

Agribusiness is swamping us with genetically altered foods, with little regard for the impact on our health and the environment.

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The use of genetic engineering in agriculture and food production has impacts not only on the environment and biodiversity but also on human health. Therefore, thorough biosafety assessment requires not only evaluation of environmental impacts of genetically engineered organisms but also assessment of the risks that genetically engineered foods pose for the health of consumers.

The hazards that may be introduced into foods through genetic engineering are threefold: allergens, toxins, and reduced nutritional quality. This paper begins with a discussion of how genetic engineering may introduce these risks into foods, and then outlines the procedures for assessing whether or not a given genetically engineered food contains such hazards. In this discussion, foods, food ingredients and food additives produced through recombinant DNA technologies will be called "genetically engineered", "recombinant" or "transgenic" foods, and the term "food" will be used to refer collectively to foods, food ingredients, food additives and nutritional supplements.

Some of the health risks associated with genetically engineered foods can be anticipated on the basis of the characteristics of the unmodified organism from which the transgenic food-producing organism was generated, and from the source of the genes used in developing the genetically engineered organism. For instance, if a gene derived from peanuts is introduced into a plant, food produced from the resulting genetically engineered plant might cause allergic reactions in people who are allergic to peanuts.

In addition to these anticipatable risks, current recombinant DNA methods—and those likely to be developed in the foreseeable future—are all capable of introducing unintended changes in the function and structure of the food-producing organism. As a result, the genetically engineered food may have characteristics that were not intended by the genetic engineer. Some of these accidental changes may be harmful to the health and safety of the consumer.

Before a genetically engineered food is placed on the market, it should be tested to ascertain that it is free of both anticipatable and unexpected allergens and toxins, and to ascertain whether or not it is altered in nutritional quality. The testing strategies presented below are designed to accomplish this objective.

HOW GENETIC ENGINEERING CAN CREATE HAZARDOUS FOODS

1. Genetic engineering introduces into foods new proteins that can either directly or indirectly threaten health.

Genetic engineering introduces new genes, new genetic information, into the cells of a food-producing organism. Since a gene is the blueprint for a protein, that new genetic information causes the organism to produce one or more new proteins. In turn, the food produced by that genetically engineered organism will contain those new proteins. Thus, genetic engineering introduces new ingredients, new constituents into foods.

The new proteins that genetic engineering introduces into foods can come from virtually any organism on Earth, and most of these new proteins will never have previously been present in significant amounts in human foods. Because people have never before eaten these proteins, the effects that they might have on health will not be known. Thus, the only way to be sure that these foods are safe is to test them thoroughly.

What might be their possible harmful effects? These new proteins could, themselves, cause allergies or be toxic. Alternatively, they could alter the cellular metabolism of the food-producing organism in unintended and unanticipated ways, and, in turn, these alterations in metabolism could cause allergens or toxins to be produced in the food.

Another possibility is that, as a result of these alterations in metabolism, the food-producing organism might fail to make some important vitamin or nutrient. Consequently,

the genetically engineered food would lack important nutrients that are normally present in the corresponding, natural, non-genetically-engineered food.

2. Genetic engineering can create dangerous foods by generating mutations in the DNA of the food-producing organism.

Inserting a recombinant gene into the DNA of a food-producing organism disrupts the natural sequence of genetic information within that DNA. Thus, the process of genetic engineering causes mutations to the food-producing organism. These mutations are a second source of potentially damaging effects of genetic engineering.

The location at which these mutations occur will be random because, by and large, genetic engineers cannot control the site at which a recombinant gene is inserted into the DNA of the organism. They can cut and splice genes in the test tube with considerable precision, but the process of inserting those recombinant genes into the host is very imprecise.

Many parts of an organism's DNA do not contain genes. Therefore, inserting a recombinant gene into such a location will not disrupt any of the genes of the organism, and, according to what molecular biologists know today, such insertions should not cause any harm. However, it is just as likely that the recombinant gene will be accidentally inserted into the middle of one of the genes of the organism. This will disrupt that gene, and the organism will no longer be able to produce the protein for which that gene is the blueprint.

That gene may be the blueprint for an enzyme that is important in cellular metabolism. Disrupting that gene could alter cellular metabolism, possibly causing the organism to produce a toxic compound that accumulates in the food produced by the organism. Disrupting metabolism could also prevent the organism from producing certain vitamins or nutrients, therefore reducing the nutritional value of the food.

Another possibility is that a genetically engineered gene might be inserted into the DNA very close to an important gene of the food-producing organism, thereby altering the expression of that gene. For instance, it could cause the food-producing organism to produce ten times more or ten times less of that protein. This could cause a variety of problems. First, a protein that is not toxic or allergenic, when present at normal levels, might become toxic or allergenic if present at ten times higher levels. Second, if an important enzyme is produced at a level ten times higher or ten times lower than normal, this could drastically alter cellular metabolism, leading to the production of a toxin or an allergen or to the inability to produce an important nutrient. Third, if the gene encodes a peptide hormone, producing it at higher or lower levels could disrupt important physiological processes, again leading to changes in food quality or safety.

There is a final problem that could result from mutations caused by genetic engineering. As mentioned above, the DNA of most organisms contains long stretches that do not serve as genes. The current view is that these sequences do not have important functions, since altering or deleting portions of them does not seem to have striking effects on the organism. However, the possibility has not been eliminated that such insertions could have unanticipated, long-term or subtle effects that might not be immediately obvious, but that could be damaging to the species or to the quality of the food that it produces. Nature is parsimonious, thus it is likely that these sequences have important functions, even though we do not presently know what those functions might be. Therefore, we should not assume that insertions into these sequences will be harmless.

3. The damaging effects of genetic engineering cannot be predicted or controlled.

The ability of genetic engineering to introduce unanticipated health hazards into foods derives from the fact that, although genetic engineers can cut and splice DNA molecules with base-pair precision in the test tube, when an altered DNA molecule is introduced into the genome of a living organism, the full range of its effects on the functioning of that organism cannot be controlled or predicted.

What this means is that, in addition to the changes in biological function intended by the genetic engineer, the introduced DNA may bring about other, unintended changes, some of which may alter the properties of the food produced by the organism in a manner that makes it damaging to health.

Proponents of biotechnology argue that the risk associated with genetically engineered foods is very small. However, there is no scientific evidence that this is the case.

Although the potential health hazards of genetically engineered foods are not different from those associated with other foods (namely, allergens, toxins and reduced nutritional value), the process of genetic engineering itself is responsible for generating these dangers; that is, the use of the genetic engineering process introduces hazards into the resultant food. Thus, the use of genetic engineering in the development of a new food-producing organism constitutes, in itself, a valid regulatory trigger. Stated in another way, because there is a distinct class of risk that is directly and uniformly associated with the process by which genetically engineered foods are produced, that process—genetic engineering—can be used as a reliable flag for identifying foods that should undergo safety testing.

Proponents of biotechnology argue that the risk associated with genetically engineered foods is very small. However, there is no scientific evidence that this is the case. If one holds to the standards of the science of risk assessment, the existing body of data allows one only to state that, for a given genetically engineered food, the risk is finite but of unpredictable magnitude. A real risk, especially one of unpredictable probability and severity, is something that requires testing.

To support the contention that risks are small, proponents attempt to infer the safety of future transgenic foods from the properties of genetically engineered foods now on the market. However, this is also not consistent with established principles of the science of risk assessment. Furthermore, even if such comparisons were valid, the handful of examples now available do not provide a sufficient database for such estimates. The diversity of possible genetic manipulations that could be carried out in the future, and the diversity of food-producing and gene-source organisms that could be employed in the genetic engineering of future foods, is extremely large. Current examples are simply not representative of the range of possibilities that will emerge in the future. Thus, to assure safety, each genetically engineered food should be tested thoroughly before it is placed on the market.

THE INABILITY TO PREDICT AND CONTROL THE OUTCOME OF GENE MANIPULATIONS

The inability of biotechnologists to fully control and predict the outcome of genetic modifications of food organisms is due to three factors: the complexity of the recipient organism; the tendency of recombinant DNA manipulations to induce mutations at random locations within the genome of the recipient organism; and the ambiguity of, and cell-type specificity of, regulatory genetic information.

1. Biological complexity leads to the inability to control or predict the effects of recombinant DNA manipulations.

An important contributor to the unpredictability of genetic engineering is the complexity of the recipient organism. The structures and functions of even the simplest single-celled microorganism are sufficiently complex that developers cannot take all components of the system into account when they consider the impact of a given genetic alteration.

In such a situation, surprises are inevitable, and many of those surprises will not be advantageous. The mechanisms by which genetic manipulations can lead to increased allergenicity and toxicity, described below, provide examples of such surprises.

2. Mutations through Recombinant DNA Manipulations.

The second source of uncertainty regarding the effects of recombinant DNA manipulations stems from the extremely crude nature of current gene transfer techniques. The genetic information introduced into the organism may be precisely defined in sequence, but it is inserted at random into the genome of the recipient organism. Each insertional event is in fact a random mutagenic event.

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Stated another way, gene transfer as it is commonly done is a mutagenic process that can disrupt any of the processes in which DNA and RNA participate. The sites at which such mutations occur will be random. Therefore, there is no way to predict which gene or regulatory processes will be disrupted as a result of gene transfer-induced mutagenesis.

By inactivating or altering the expression of genes encoding enzymes that catalyse important biosynthetic processes, mutagenic events could alter the allergenicity of a food or make it toxic, as described in detail below. These mutagenic events could also alter the nutritional qualities of a food. Furthermore, by altering regulatory sequences present normally in the recipient organism's genome, the same variety of regulatory sequence-related problems described below could be generated.

It should be pointed out that with most gene transfer methods used in eukaryotes, this mutational process will occur not just sometimes but *every* time a recombinant gene is inserted into the genome of an organism. Each such insertional event disrupts some native DNA sequence. Many such disruptions will, fortunately, be silent or inconsequential. However, there is a finite chance that one of these will alter the structure or function of the organism in a manner that significantly influences the properties of the foodstuff derived from it. That is, genetic alterations have a finite probability of altering the properties of the organism, such that the properties of the food derived from it will be hazardous to health. In most cases, the procedures used in modification of food-producing organisms insert not one but *several* copies of a gene into the genome of the recipient organism. Thus, multiple random mutagenic events may occur, greatly increasing the probability of damaging some gene important to food quality.

The risks related to manipulating the genomes of food-producing organisms are inherent in the mechanisms by which recombinant DNA techniques bring about genetic change. These risks cannot be discounted by pointing to the "FlavrSavr" tomato (the first genetically engineered crop to be commercialised) and saying that there have been no problems with it and therefore other transgenics will probably be safe, too. Each transgenic food-producing organism will undergo different mutagenic events and respond to the genetic information introduced into it differently, leading to the range of unexpected alterations described above. Therefore, there is no scientifically valid justification for such extrapolations.

3. Ambiguities of Genetic Information.

Genes contain two distinct kinds of information: structural and regulatory. Structural information specifies the amino acid sequence of proteins and consists of the genetic code, which was elucidated in the 1960s. With a few exceptions, this code is identical for all terrestrial organisms. Thus, the structural information contained in a given piece of DNA is predictable.

However, the story is quite different for regulatory information. Transcription, translation, replication, recombination and other processes involving DNA and RNA are controlled by regulatory information encoded in DNA or RNA sequences.

The regulatory decoder is much more complex and diverse than the structural code. Furthermore, it is different in different organisms, and is even different in different cell types of the same organism. For instance, there are many examples in the molecular biological literature in which recombinant genes, characterised in one cell type, are expressed at 100-fold or even 1,000-fold higher levels in another cell type from the same organism. Such differences cannot be predicted simply by knowing the nucleic acid sequence of a recombinant gene. The only way to know is to gather empirical information—by actually introducing the gene into the second cell type and examining the result.

If this is the case for different cell types within a single organism, the level of unpredictability will certainly be as great or greater for cross-species transfers of the kind commonly carried out in agricultural genetic engineering.

The underlying mechanism involved in the 'reading' of regulatory information is well understood. Regulatory proteins exist in the cell, each of which is capable of scanning DNA (or RNA) molecules. Each can recognise and bind to a single, specific nucleic acid motif. That binding reaction triggers biochemical events leading to modulation of a process such as transcription, translation, replication, recombination, etc. In any particular cell, a given sequence can influence one of these processes only if the protein that recognises that sequence is also present. Since different regulatory proteins are expressed in different cell types and in different species, a given DNA sequence will function as a regulatory signal only in some cell types and some species, and not in others. Our knowledge of the 'regulatory code' is extremely

incomplete. Therefore, we cannot examine the sequence of a nucleic acid molecule and predict its regulatory function in a given organism.

Inserting DNA sequences that possess unanticipated regulatory activities into the genome of a food-producing organism could disrupt any of the cellular processes in which DNA or RNA participate, including replication, transcription, translation, recombination and transposition.

Disruption of transcription or translation could alter the level of expression or the timing of the expression of any protein that is normally expressed in a food-producing organism. This could alter the allergenicity or toxicity of the food derived from that organism, as described below, and could also alter its nutritional or other characteristics.

Disruption or alteration of replication, recombination or transposition mechanisms could, among other things, alter the plasticity or stability of the recipient organism's genome, leading to increased rates of mutagenesis and consequently to a range of problems, as described below.

ALLERGENS GENERATED IN RECOMBINANT FOODS

There exist several mechanisms by which allergens could be expressed in foods through genetic engineering. A number of molecular mechanisms have also been identified through which the genetic manipulation of food-producing organisms could generate new allergens or increase the allergenicity of proteins normally present in food-producing organisms.

Because allergen-carrying transgenic foods will in most cases maintain the appearance of their natural, non-allergenic counterparts, they pose a serious hazard to the consumer. Consumers will not be able to avoid these allergenic foods because they will not be able to distinguish them from the corresponding natural foods. The labelling of all genetically engineered foods could, of course, solve this problem and would also make it possible for health authorities to trace allergen problems that arise.

Because allergen-carrying transgenic foods will in most cases maintain the appearance of their natural, non-allergenic counterparts, they pose a serious hazard to the consumer.

At present, empirical evidence regarding the generation of allergenic foods through genetic engineering is sparse, since few of the genetically engineered foods now under development have been thoroughly tested for allergenicity. However, one example has already come to light.

Pioneer Hybrid has developed soybeans with a nutritionally balanced amino acid composition. They accomplished this by engineering into these beans the gene for a brazil nut storage protein. However, this protein turns out to be allergenic to a significant proportion of the population. Pioneer Hybrid has wisely decided to terminate plans to commercialise this product.

TOXINS AND IRRITANTS GENERATED IN RECOMBINANT FOODS

Most substances that will occur in foods as a result of genetic engineering will be proteins that will be present in only trace concentrations. Nevertheless, those added components, in even trace amounts, may substantially alter either the nutritional or other biological characteristics of the food.

In addition to allergenicity, recombinant proteins could manifest a variety of other biological activities, and, in the case of recombinant enzymes, could catalyse the production of other compounds with biological activities not normally present in a particular food. For instance, such substances could act as toxins, irritants, hormone mimetics, etc., and could act at the biochemical, cellular, tissue or organ levels to disrupt a range of physiological functions.

An example of a class of genetically engineered foods of particular concern are those that have been modified to produce biological control agents, such as the family of insecticidal Bt enterotoxins. Each of the Bt toxins is specific for a certain class of insects. The Btk toxin, which has been used topically in organic farming for many years, has not been reported to cause toxic reactions in consumers when used in this way. However, it would not be surprising if a compound such as Btk toxin, which has powerful biological activity in one class of organisms, might also have some biological activity even in a distant phylum such as the vertebrates. Such activity might become apparent if the toxin is consumed in larger amounts, as will occur in transgenic foods derived from organisms engineered to express this toxin constitutively at high levels.

Normally when used topically, Bt toxin is degraded to undetectable levels by solar UV light and other mechanisms in just a few days. However, Bt-engineered plants produce this toxin continually, resulting in much higher steady-state levels. Furthermore, the toxin will be present not only on the surface of the plant but internally where, protected from UV light degradation, it may accumulate.

The result is that consumers of these foods may take in much larger amounts of Bt toxin than is the case with foods derived from topically-treated plants. Consequently, the excellent safety record of topically-applied Bt toxin does not constitute reliable evidence indicating that foods derived from plants genetically engineered to produce Bt toxin will be safe. ∞

About the Author:

Dr John Fagan has spent more than 24 years using cutting-edge molecular genetic techniques in cancer research. He earned a B.Sc. (*cum laude* with distinction in chemistry) from the University of Washington and a Ph.D. in biochemistry and molecular biology from Cornell University. He has authored more than 50 technical articles, which have been published in international, peer-reviewed journals including *Biochemistry* and *Molecular and Cellular Biology*. A biochemistry professor at Maharishi University, he recently published *Genetic Engineering: The Hazards; Vedic Engineering: The Solutions.*

In recent years Dr Fagan has been increasingly concerned about the dangers of genetically engineered foods, the hazards of releasing genetically engineered organisms into the environment, and the risks of germline genetic engineering in humans. In November 1994 he took an ethical stand against these applications, urging scientists to take safer, more productive research directions and to focus more on prevention and less on high-tech therapeutics. He underscored these warnings by returning a US$613,882 grant to the National Institutes of Health and withdrawing grant applications worth another US$1.25 million.

Currently, Dr Fagan is conducting a global campaign to alert the public to the hazards of genetically engineered foods. His goal is to reshape national and international policy and regulations regarding the safety, testing, labelling and importation of genetically engineered foods.